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# Differential Effects of Angiotensin Converting Enzyme Inhibition and Diuretic Therapy on Reductions in Ambulatory Blood Pressure, Left Ventricular Mass, and Vascular Hypertrophy

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Diuretic-based therapy is less effective in reducing the cardiac complications of hypertension than the risk of stroke and may be less effective in reducing left ventricular (LV) mass than is therapy with angiotensin converting enzyme (ACE) inhibition. In view of the strong association of LV hypertrophy with cardiovascular risk, this study was designed to compare the impact of therapy with a diuretic and ACE inhibition on cardiac and vascular structure.

Fifty essential hypertensives (74% male, 88% nonwhite) participated in a double-blind study for 6 months and were randomized to either ramipril or hydrochlorothiazide (HCTZ). Echocardiography, carotid ultrasonography, and ambulatory blood pressure (BP) monitoring were performed at baseline and 3 and 6 months after initiation of therapy. The 22 ramipril patients were comparable to the 28 HCTZ patients at baseline in age, race, and 24-h BP. Although HCTZ resulted in a greater reduction in 24-h BP, only treatment with ramipril resulted in a decrease in LV mass (193 to 179 g,  $P < .005$ ,  $v$  184 to 182 g,  $P = \text{NS}$ ), attributable to a reduction in wall thicknesses but not in chamber diameter. In

multivariate analysis, both change in BP and treatment group were independent predictors of change in LV mass. Importantly, although neither drug reduced carotid artery cross-sectional area, relative wall thickness increased due to a tendency for vessel diameter to decrease and wall thickness to increase, particularly in the diuretic group. Ramipril caused a sustained fall in plasma angiotensin II, whereas HCTZ increased angiotensin II levels.

Although diuretic therapy was more effective in lowering ambulatory BP in this predominantly nonwhite population, only therapy with ACE inhibition was associated with regression of LV mass. Vascular geometry was altered consistent with the reduction in distending pressure resulting in vascular remodelling. *Am J Hypertens* 1998; 11:387-396 © 1998 American Journal of Hypertension, Ltd.

**KEY WORDS:** Angiotensin converting enzyme inhibition, ambulatory blood pressure, echocardiography, hypertension, left ventricular hypertrophy, carotid artery.

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**D**iuretic-based regimens for the treatment of hypertension reduce blood pressure and reduce overall cardiovascular disease event rates in hypertensive patients compared to placebo. However, this benefit has been especially due to stroke prevention, and results with regard to prevention of cardiac complications of hypertension have been less impressive.<sup>1,2</sup> Although metabolic side effects of diuretics have been implicated, one potentially cardiotoxic action of these agents that has received relatively little attention is their activation of the renin-angiotensin system. Low renin activity has been associated with a low prevalence of hypertensive complications,<sup>3</sup> whereas high renin status as well as augmentation of plasma renin activity by a low-salt diet have been shown to predict myocardial infarction independently of blood pressure or other risk factors in hypertensive patients.<sup>4-6</sup>

Left ventricular mass is a stronger predictor of morbid and mortal complications of hypertension than blood pressure or all other risk factors except age itself<sup>7-11</sup> and the data, mostly from short-term and small-sized studies, suggest that antirenin system therapy with angiotensin converting enzyme (ACE) inhibitors may reduce left ventricular mass more than expected for the degree of blood pressure lowering in hypertensive patients,<sup>12-15</sup> animals,<sup>16,17</sup> and in patients with end-stage renal disease.<sup>18</sup> ACE inhibitors have also been suggested, in studies using relatively limited methods, to have more beneficial effects on arterial stiffness—a variable that may influence the load on the heart independently of mean blood pressure—than other types of antihypertensive agents.<sup>19</sup> However, few comparative studies of the cardiac effects of antihypertensive drugs have taken into account the potentially important effects on LV mass of ambulatory blood pressure,<sup>20</sup> arterial stiffness,<sup>18,21</sup> and variations in stroke volume.<sup>18,22</sup> Furthermore, the relative impacts of antihypertensive agents on large vessel hypertrophy in hypertension are unknown. Accordingly, the present study was undertaken to compare the effects on cardiovascular structure of a representative ACE inhibitor, ramipril, and of hydrochlorothiazide, a prototypic diuretic.

## METHODS

**Study Design** A screening echocardiogram was performed at The New York Hospital—Cornell Medical Center to verify that it was possible to obtain echocardiograms of sufficiently high quality in a participant to be reproducible over time. In accord with our previous suggestion,<sup>23</sup> individuals with elevated left ventricular mass and ones with normal mass were both included in the study. To prevent the expected reduction of initially high ventricular mass values over time due to regression to the mean of qualifying measure-

ments that are required to exceed a predetermined partition value,<sup>24</sup> a separate baseline echocardiogram was performed in all participants to document the ability to obtain high-quality left ventricular images. Eligible subjects underwent full evaluation including, in addition to echocardiography, carotid ultrasonography, 24-h ambulatory blood pressure determination, and measurement of plasma renin activity, angiotensin II levels, and 24-h urinary sodium and albumin excretion at baseline before beginning randomly assigned therapy, and after 3 and 6 months of treatment.

Study medication was begun at a dose of 5 mg ramipril or 12.5 mg hydrochlorothiazide once a day. If arterial pressure was not controlled (seated diastolic blood pressure reduction by at least 7% and to a level  $\leq 100$  mm Hg), the blinded study medication was doubled after 2 and 4 weeks to a maximum dose of 20 mg/day ramipril or 50 mg/day hydrochlorothiazide.

**Study Population** Study subjects were recruited between June, 1993, and September, 1995, from a population of employed adults enrolled in a worksite-based hypertension detection and treatment program that has been previously described.<sup>25,26</sup> Eligibility criteria included seated diastolic blood pressure of 95 to 114 mm Hg when not being treated or following a 4-week placebo washout period. Of a total of 82 subjects who underwent screening echocardiography, eight were excluded because of technically limited echocardiograms, four were excluded because it was found after the screening echocardiogram that they did not meet other inclusion/exclusion criteria and three decided that they did not want to enter the trial. An additional seven patients in whom technically adequate echocardiograms showed normal left ventricular mass were not enrolled in the study because the *a priori* target for this study arm had already been achieved. Of the total of 60 subjects enrolled in this randomized, double-blind trial, seven were discontinued before the end of the planned 6-month study duration because of inability to control blood pressure by the maximum dose of blinded study medication, two because of apparent intolerance to study medication, and one because of withdrawal of consent.

All patients were asymptomatic and free of clinical evidence of cardiovascular disease other than hypertension. In the 34 patients (68%) who had previously received pharmacologic antihypertensive therapy, medications were stopped for at least 4 weeks before the baseline ambulatory monitoring and ultrasound studies. Patients requiring other vasoactive medications were excluded from the study. Blood specimens were obtained after an overnight fast, and serum lipids and electrolytes were measured using standard techniques. The study was performed using protocols

approved by the Institutional Review Boards of Albert Einstein College of Medicine and Cornell University Medical College. All patients gave written, informed consent to participate in the study.

**Blood Pressure Determination** Ambulatory blood pressure recording was performed over a 24-h typical day in all subjects using a SpaceLabs (Redmond, WA) 90207 monitor. As previously described,<sup>27</sup> readings were obtained every 15 min during the day and every 30 to 60 min at night. Patients were instructed to note their activity in a diary. Blood pressure recordings were classified according to activity using custom-written software and averaged to reflect actual awake and sleep periods. Basal blood pressure was defined as that taken on the completion of the ultrasound studies, ie, after approximately 1 h of supine rest in a darkened, quiet room.

**Echocardiography** All echocardiograms were performed by a single highly experienced research technician using standard techniques. Strip-chart recordings were coded by the technician and measured by a single, blinded observer using a digitizing tablet. Left ventricular dimensions were measured according to American Society of Echocardiography recommendations.<sup>28</sup> Left ventricular mass (LVM) was calculated using the formula:  $LVM = 0.8 (1.04[LVID_d + IVS_d + PWT_d]^3 - [LVID_d]^3) + 0.6$  g, where LVID is left ventricular internal dimension, PWT is posterior wall thickness, IVS is inter-ventricular septal thickness and subscripted d indicates end-diastole.<sup>29</sup> Whenever the left ventricle was imaged from too low a window to obtain optimal M-mode recordings, ventricular measurements were obtained from the two-dimensional study using American Society of Echocardiography recommendations.<sup>30</sup> Left ventricular function was assessed by calculation of fractional shortening (FS):  $FS = (LVID_d - LVID_s)/LVID_d$ , where LVID<sub>d</sub> and LVID<sub>s</sub> are end-diastolic and end-systolic diameters, respectively. Left ventricular hypertrophy was considered to be present if the mass index exceeded 51 g/m<sup>2.7</sup>, a partition value that may optimally predict cardiovascular risk in hypertension.<sup>31</sup> Left ventricular geometry was classified using left ventricular mass index and relative wall thickness,<sup>32</sup> using a relative wall thickness partition value of 0.45. Stroke volume was calculated by multiplying the time velocity integral of flow in the left ventricular outflow tract by the area of the left ventricular outflow tract. Patients with valvular stenosis or more than mild valvular regurgitation by Doppler echocardiography were excluded from the study.

**Carotid Ultrasonography** Imaging of the right and left extracranial carotid arteries was performed by the same research technician using a 7.0 or 7.5 MHz transducer with the patient supine with slight hyperextension of the neck. The arteries were scanned for the

presence of discrete carotid atherosclerotic plaque.<sup>33</sup> An M-mode tracing of the distal left common carotid artery was recorded on videotape. Measurement of the intimal-medial thickness of the far wall at end-diastole and continuous tracing of the lumen-intima interface of the near and far walls was performed using a frame-grabber attached to a high resolution monitor using previously described techniques.<sup>34,35</sup> Measurements were performed on several cycles and averaged. Wall thickness and lumen measurements were never made at the level of a discrete plaque. Arterial relative wall thickness (ARWT) was calculated as:  $ARWT = 2 \times \text{wall thickness}/\text{end-diastolic diameter}$ . Vascular strain (VS) was calculated according to the formula:  $VS = (D_s - D_d)/D_d \times 100$ , where D<sub>s</sub> and D<sub>d</sub> are common carotid artery peak-systolic (maximum) and end-diastolic (minimum) diameters, respectively. Supine brachial blood pressure was taken in triplicate by the technician at the termination of the ultrasound studies using an appropriately sized cuff and mercury sphygmomanometer. These readings were averaged to get the basal blood pressure.

**Renin-Angiotensin System Assessment** Twenty-four hour urine collections were completed on the morning the ultrasound studies were performed. Plasma samples for determination of renin activity and angiotensin II levels were obtained from previously ambulatory patients in the seated position. Measurements of plasma renin activity and plasma angiotensin II levels were performed as previously described.<sup>36,37</sup> An HPLC step was included in the angiotensin II assay prior to the radioimmunoassay.

**Statistical Methods** Data are presented as mean values with one standard deviation as the index of dispersion. Mean values in the two treatment groups were compared using an independent-samples *t* test. Categorical variables were compared using  $\chi^2$  analysis. The relation of continuous variables was assessed using linear regression (general linear model in SPSS 6, SPSS, Inc., Chicago, IL). Independent correlates of the changes from baseline in left ventricular mass were identified using multiple linear regression analysis with an enter procedure.

## RESULTS

**Baseline Characteristics** A total of 50 patients completed the 6 month study. The 37 men and 13 women had a mean age of  $51.2 \pm 7.4$  years (range 38 to 69). Eighty-eight percent of the patients were nonwhite: 66% black (American or Caribbean), 18% Hispanic, and 4% Asian Indian.

The 13 patients with and the 37 patients without left ventricular hypertrophy did not differ with regard to age, gender, race, body habitus, conventional laboratory parameters, or measures of the activity of the



TABLE 1. COMPARISON OF BASELINE CHARACTERISTICS OF PATIENTS TREATED WITH RAMIPRIL VERSUS HYDROCHLOROTHIAZIDE

Variable	Ramipril (n = 22)	P	Hydrochlorothiazide (n = 28)
Age (years)	52.7 ± 6.9	NS	50.1 ± 7.7
Gender (% male)	59	<.05	86
Race (% nonwhite)	91	NS	86
Height (in.)	65.6 ± 4.3	<.01	68.6 ± 3.0
Weight (lb.)	171.5 ± 33.1	NS	186.0 ± 30.9
Body surface area (m <sup>2</sup> )	1.86 ± 0.23	<.05	1.99 ± 0.19
Body mass index (kg/m <sup>2</sup> )	27.8 ± 3.0	NS	27.7 ± 3.6
Basal blood pressure (mm Hg)	153/94	NS	146/95
24-h blood pressure (mm Hg)	153/96	NS	146/93
Awake blood pressure (mm Hg)	155/98	NS	149/96
Sleep blood pressure (mm Hg)	142/87	<.05	134/82
Left ventricular			
Septum (cm)	1.09 ± 0.12	NS	1.05 ± 0.16
Posterior wall (cm)	0.99 ± 0.11	NS	0.96 ± 0.13
Diastolic diameter (cm)	5.00 ± 0.51	NS	5.00 ± 0.42
Mass (g)	193.5 ± 46.6	NS	184.4 ± 42.4
Mass index (g/m <sup>2</sup> )	103.6 ± 20.3	NS	92.7 ± 19.9
Mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> )	48.5 ± 10.2	<.01	41.1 ± 9.0
Fractional shortening (%)	37 ± 8	NS	36 ± 6
Common carotid artery			
Intimal-medial thickness (mm)	0.77 ± 0.14	NS	0.75 ± 0.15
Cross-sectional area (mm <sup>2</sup> )	15.6 ± 4.3	NS	15.4 ± 3.9
Strain (%)	12.1 ± 2.9	NS	11.0 ± 3.4

renin-angiotensin system. In contrast, the patients with increased ventricular mass had higher basal (159/98 *v* 146/93 mm Hg, *P* < .01 for systolic pressure) and ambulatory blood pressure levels (24-h pressure: 157/99 *v* 146/93 mm Hg, *P* < .05; awake pressure: 160/101 *v* 149/96 mm Hg, *P* < .05). As expected, all left ventricular dimensions, as well as calculated ventricular mass (235.2 *v* 171.8 g) and mass indices (58.4 *v* 39.5 g/ht<sup>2.7</sup>) were higher in the individuals with left ventricular hypertrophy.

Randomized treatment assignment resulted in 28 of the patients who completed the 6 month study receiving hydrochlorothiazide and 22 receiving ramipril. As may be seen in Table 1, a higher proportion of the ramipril-treated patients were women, as a consequence of which body height, weight, and body surface area—but not body mass index—were smaller in this group. The levels of conventional laboratory variables and measures of renin-angiotensin system activity were statistically indistinguishable between these groups. The patients assigned to receive ramipril had slightly higher blood pressures than did those randomized to the hydrochlorothiazide arm of the study, but only the differences in sleep blood pressure achieved statistical significance. The ramipril-treated patients also had slightly, but generally insignificantly, higher levels for each of the primary left ventricular measurements and calculated indices of ven-

tricular hypertrophy. The two groups did not differ in vascular structure or function.

**Effects on Renin-Angiotensin System Activity and Blood Pressure** As may be seen in Table 2, therapy with hydrochlorothiazide resulted in a significant reduction in serum potassium and slight increases in serum creatinine, glucose and total cholesterol concentrations, whereas these values remained stable in the ramipril-treated patients. Treatment with ramipril resulted in a significant and sustained reduction of plasma angiotensin II levels and hydrochlorothiazide caused a directionally opposite trend, with a highly significant between-groups difference by repeated measures analysis of variance, whereas both agents caused similar increases in plasma renin activity.

Highly significant decreases in arterial pressure obtained at the completion of the ultrasound studies (basal blood pressure) occurred in the diuretic-treated patients but not in those who received ramipril. In contrast, both 24-h and day and night systolic and diastolic pressures were significantly reduced by ramipril, but fell even more in hydrochlorothiazide-treated patients. Furthermore, the percent change in the 24-h ambulatory blood pressure was significantly greater in the hydrochlorothiazide-treated group (24-h pressure: -9.1/-9.1% *v* -3.2/-4.4%, *P* < .05).

TABLE 2. IMPACT OF DRUG THERAPY ON RENIN-ANGIOTENSIN SYSTEM AND BLOOD PRESSURE

Variable	Ramipril				Hydrochlorothiazide			
	Baseline	3 month	6 month	P	Baseline	3 month	6 month	P
Sodium (mEq/L)	141.2 ± 2.5	141.1 ± 2.5	141 ± 2.3	NS	140.2 ± 1.3	140.1 ± 1.5	140.0 ± 1.5	NS
Potassium (mEq/L)	4.16 ± 0.35	4.22 ± 0.27	4.22 ± 0.29	NS	4.20 ± 0.38	3.87 ± 0.53	3.87 ± 0.40	<.005
Creatinine (mg/dL)	1.06 ± 0.25	1.05 ± 0.20	1.09 ± 0.27	NS	1.11 ± 0.20	1.15 ± 0.19	1.19 ± 0.23	<.05
Glucose (mg/dL)	92.1 ± 9.6	96.5 ± 16.9	97.3 ± 12.0	NS	90.4 ± 11.6	88.4 ± 15.2	98.7 ± 21.4	NS (.06)
Cholesterol (mg/dL)	211 ± 30	217 ± 37	218 ± 31	NS	201 ± 37	211 ± 36	215 ± 38	<.05
PRA (ng AI/mL/h)	0.96 ± 1.50	1.98 ± 3.07	2.04 ± 2.51	<.01	0.73 ± 0.92	2.06 ± 2.08	1.51 ± 1.75	<.005
Angiotensin II (ng/mL)	2.26 ± 3.94	0.96 ± 2.36	0.84 ± 1.41	<.05	2.20 ± 3.06	5.65 ± 7.22	4.42 ± 6.90	NS (.06)
Basal BP (mm Hg)	153/94	148/90	147/91	NS	146/95	136/90	136/88	<.001
24-h BP (mm Hg)	153/96	144/89	147/91	<.001	146/93	136/86	132/84	<.001
Awake BP (mm Hg)	155/98	147/92	150/94	<.005	149/96	139/90	136/88	<.001
Sleep BP (mm Hg)	142/87	133/81	136/82	<.01	134/82	123/75	121/74	<.001

PRA, plasma renin activity; BP, blood pressure.

**Effects on the Left Ventricle and Common Carotid Artery** There were small decreases in left ventricular wall thickness and mass during hydrochlorothiazide treatment that did not attain statistical significance (Table 3). In contrast, decreases in left ventricular wall thickness, but not in chamber size, resulted in substantial reductions in left ventricular mass in the ramipril-treated patients after 3 and 6 months of taking the study medication (Figure 1). The strongest univariate correlates of the percent change in left ventricular mass were the percent change in basal systolic ( $r = 0.47$ ,  $P < .0005$ ) and diastolic ( $r = 0.44$ ,  $P = .001$ ) blood pressures and the initial level of left ventricular mass ( $r = -0.30$ ,  $P < .05$ ). In multivariate analyses, the change in left ventricular mass was predicted by the change in either basal systolic or diastolic blood pressure ( $P < .0005$  for both), and independently by the assigned treatment group ( $P =$

.05). There were no changes in left ventricular stroke volume in either group.

Although there were no significant changes associated with either drug in carotid artery size or vascular strain, relative wall thickness of the vessel significantly increased in the diuretic-treated group due to a strong tendency for vessel diameter to decrease and wall thickness to increase (Figure 2). Arterial cross-sectional area tended to increase in both drug groups, although the changes did not achieve statistical significance.

## DISCUSSION

In the present study, short-term antihypertensive therapy with an ACE inhibitor and suppression of angiotensin II levels resulted in a marked reduction in left ventricular mass during short-term therapy due to a decrease in wall thicknesses. In contrast, significantly

TABLE 3. IMPACT OF DRUG THERAPY ON LEFT VENTRICLE AND CAROTID ARTERY

Variable	Ramipril				Hydrochlorothiazide			
	Baseline	3 month	6 month	P	Baseline	3 month	6 month	P
Left ventricular								
Septum (cm)	1.09 ± 0.12	1.00 ± 0.12	1.04 ± 0.13	<.05	1.06 ± 0.16	1.03 ± 0.13	1.02 ± 0.10	NS
Posterior wall (cm)	0.99 ± 0.11	0.90 ± 0.12	0.93 ± 0.12	<.05	0.96 ± 0.13	0.94 ± 0.11	0.93 ± 0.16	NS
Diastolic diameter (cm)	5.00 ± 0.51	5.02 ± 0.63	4.98 ± 0.55	NS	5.00 ± 0.42	4.99 ± 0.41	5.07 ± 0.47	NS
Mass (g)	193.2 ± 46.6	172.5 ± 45.5	179.1 ± 47.9	<.005	184.4 ± 42.4	178.3 ± 38.0	181.8 ± 47.1	NS
Mass index (g/m <sup>2</sup> )	103.6 ± 20.3	92.0 ± 18.9	94.9 ± 19.9	<.001	92.7 ± 19.9	90.9 ± 19.4	91.9 ± 23.3	NS
Mass/height <sup>2.7</sup> (g/m <sup>2.7</sup> )	48.5 ± 10.2	43.2 ± 9.2	44.8 ± 9.5	<.005	41.1 ± 9.0	40.0 ± 8.85	40.9 ± 11.6	NS
Stroke volume (mL)	67.6 ± 14.4	66.4 ± 11.2	67.3 ± 15.3	NS	72.2 ± 12.2	71.6 ± 12.5	74.8 ± 17.9	NS
Common carotid artery								
IMT (mm)	0.77 ± 0.14	0.77 ± 0.18	0.82 ± 0.13	NS	0.75 ± 0.15	0.83 ± 0.17	0.83 ± 0.24	NS
Diastolic diameter (mm)	5.61 ± 0.73	5.67 ± 0.61	5.58 ± 0.61	NS	5.74 ± 0.70	5.53 ± 0.65	5.56 ± 0.75	NS
CSA (mm <sup>2</sup> )	15.6 ± 4.3	15.9 ± 4.1	16.6 ± 3.6	NS	15.4 ± 3.9	16.6 ± 4.5	17.0 ± 6.1	NS
Relative wall thickness	0.28 ± 0.05	0.28 ± 0.08	0.30 ± 0.05	NS	0.27 ± 0.06	0.30 ± 0.06	0.30 ± 0.09	<.05
Strain (%)	12.1 ± 2.9	12.3 ± 4.9	12.8 ± 4.4	NS	11.0 ± 3.4	12.0 ± 3.4	11.6 ± 3.3	NS

IMT, intimal-medial thickness; CSA, cross-sectional area.

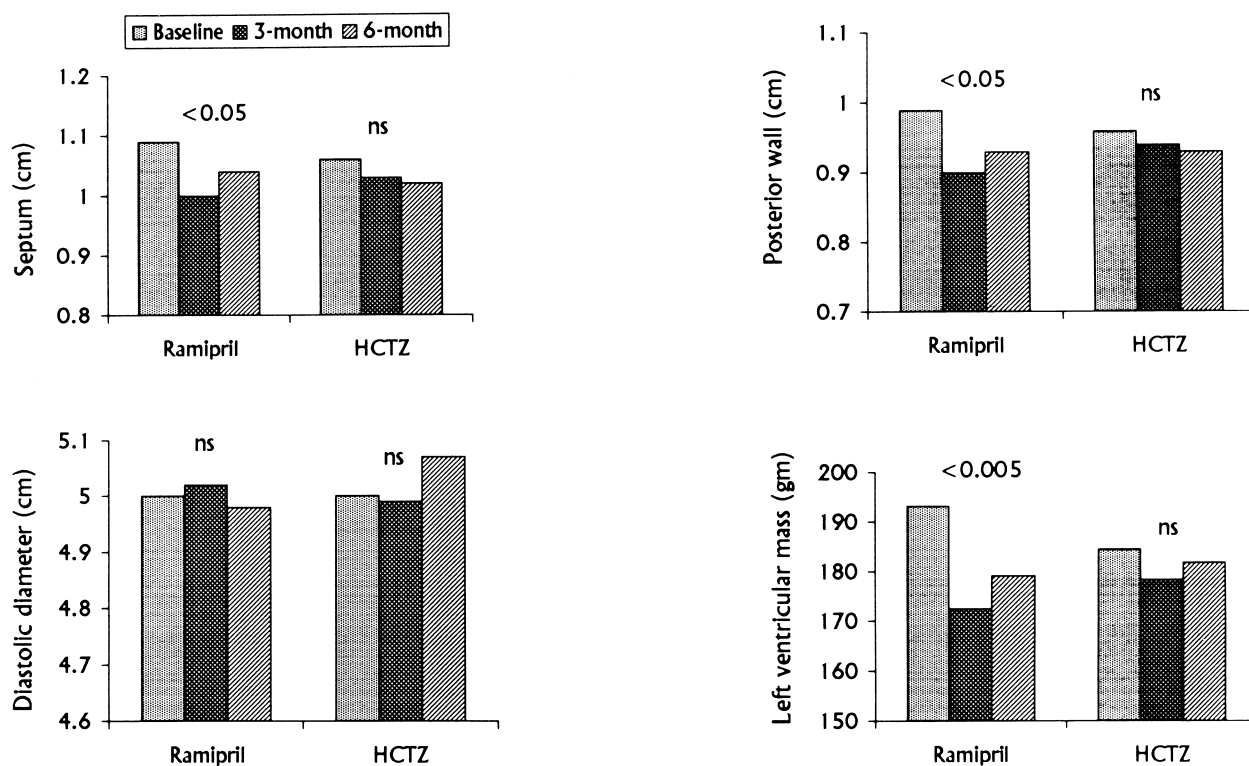


FIGURE 1. Impact of drug therapy on left ventricular wall thicknesses, chamber size and mass. HCTZ, hydrochlorothiazide.

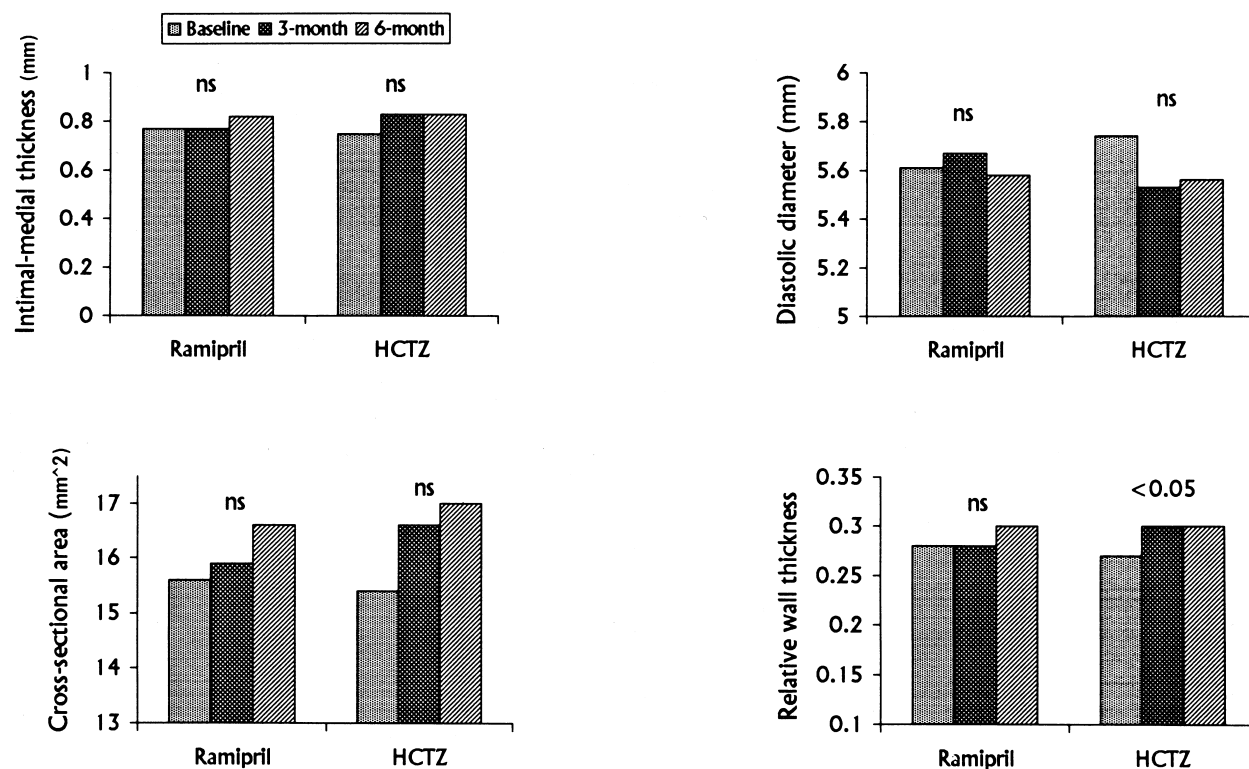


FIGURE 2. Impact of drug therapy on carotid artery structure. HCTZ, hydrochlorothiazide.

greater ( $P < .05$ ) lowering of 24-h ambulatory blood pressure with a diuretic resulted in no change in left ventricular mass. Neither class of antihypertensive therapy reduced vascular size. In fact, arterial cross-sectional area, a measure of vascular mass, tended to increase in both treatment groups due to slight increases in vessel wall thickness. A significant increase in vascular relative wall thickness (concentric remodeling) developed in the diuretic group. Our study supports the importance of the trophic influence of angiotensin II on cardiac myocytes and suggests that hemodynamic factors may be of greater relevance in determining changes in vascular structure.

The finding with regard to left ventricular mass is in keeping with two previous metaanalyses indicating that the greatest reduction in left ventricular mass was associated with ACE inhibitor therapy.<sup>12,14</sup> While the magnitude of decrease in left ventricular mass with ramipril (7.3%) and hydrochlorothiazide (1.3%) was lower than previously detected on average in other randomized, double-blind studies (13.5% with ACE inhibitors and 7.8% with diuretics<sup>14</sup>), the extent of blood pressure lowering was also less in the current study.

The use of ambulatory, rather than clinic, blood pressure in the current study increased the accuracy of determination of overall hemodynamic burden and its relation to left ventricular mass.<sup>20</sup> Although the importance of blood pressure reduction in determining the extent of regression of left ventricular mass was confirmed in the present study, the study clearly documented that factors other than blood pressure influence the degree to which left ventricular mass is reduced. In a metaanalysis confined to randomized, double-blind studies, Schmieder et al found that, in addition to the extent of blood pressure lowering, duration of antihypertensive therapy and degree of pretreatment left ventricular hypertrophy were directly related to magnitude of regression.<sup>14</sup> The latter observation was also confirmed by univariate analysis in the present study, although in multivariate analyses initial left ventricular mass was not an independent predictor of the extent of regression.

Similar to the results of the present study, the metaanalysis by Schmieder et al<sup>14</sup> also found that drug class was important in the extent of regression of left ventricular mass, with ACE inhibitors being significantly better than  $\beta$ -blockers and tending to be better than diuretics ( $P = .08$ ) and calcium channel blockers ( $P = .12$ ), whereas the latter three drug classes were equally efficacious. The recently reported Veterans Administration monotherapy trial found that the greatest reduction in left ventricular mass, after control for appropriate covariates, was achieved by an ACE inhibitor and a diuretic, with lesser effects of the studied calcium blocker and  $\beta$ -blocker.<sup>38</sup> The lack of a

greater effect on ventricular mass by the ACE inhibitor might have been due to use of a short-acting ACE inhibitor (captopril) on a twice-a-day schedule. The apparent superiority of a diuretic in the Treatment of Mild Hypertension Study<sup>39</sup> is difficult to interpret because the groups assigned to placebo pills became normotensive (mean blood pressure = 133/82 mm Hg) with very normal ventricular mass (mean = 178 g), leaving neither hypertension nor left ventricular hypertrophy for the drugs to treat.

The mechanism underlying the apparent greater magnitude of left ventricular regression with ACE inhibition in comparison to other drug classes is not entirely clear. In some animal studies, doses of ramipril that did not significantly lower blood pressure under anesthesia in rats with suprarenal aortic banding<sup>16</sup> or pulmonary artery banding<sup>40</sup> resulted in the prevention or reversal of cardiac hypertrophy. However a subsequent study suggested that blood pressure lowering was necessary for the beneficial effect of ramipril on left ventricular mass.<sup>17</sup> Although the addition of 1.25 or 5 mg ramipril to 20 mg furosemide in human hypertensives resulted in a greater decrease in left ventricular mass than placebo added to furosemide, the addition of ramipril tended to cause greater blood pressure lowering, which may have influenced study findings.<sup>15</sup> The extent to which a pressure-independent mechanism of ACE inhibition of reducing vascular hypertrophy or left ventricular mass relates to antagonism of direct trophic effects of angiotensin II on vascular smooth muscle or cardiac myocytes, detected in experimental models,<sup>41,42</sup> is uncertain.

The association of hypertension with hypertrophy of the capacitance, as opposed to resistance, vessels is well-established, and recent advances in noninvasive imaging technology have permitted in vivo quantification of its nature and extent in controlled studies.<sup>34,35,43,44</sup> In addition, increased plasma ACE activity<sup>45</sup> and certain ACE gene polymorphisms<sup>46</sup> have been associated with hypertrophy of the common carotid artery independently of blood pressure. Although numerous studies have evaluated the impact of antihypertensive therapy on the functional characteristics of the capacitance vessels, such as vascular compliance, information regarding the impact of therapy on structural changes in these large arteries in humans is lacking. In spontaneously hypertensive rats, both calcium channel blockers<sup>47,48</sup> and ACE inhibitors have been effective in reducing vascular hypertrophy, whereas vasodilators and  $\beta$ -blockers have not.<sup>49</sup> In the present study, neither form of antihypertensive therapy resulted in a change in overall vessel size (cross-sectional area), but vascular remodeling with increased relative wall thickness, which achieved statistical significance in the diuretic-treated group,



occurred as a consequence of the tendency for vessel diameter to decrease and intimal-medial thickness to increase.

The response of the capacitance vasculature to blood pressure reduction may be variable and unpredictable. Large vessel hypertrophy in hypertension appears to occur as a consequence of both an increase in vessel diameter and in wall thickness.<sup>35</sup> Whether the increase in wall thickness reflects "early atherosclerosis" due to intimal thickening or an increase in smooth muscle mass resulting in medial hypertrophy, or a combination of both processes, is unknown and may vary among individuals. By conservation of mass, a reduction in the distending pressure by any antihypertensive medication may acutely cause the vessel diameter to decrease and the wall thickness to increase. Alternatively, medications that specifically relax smooth muscle cells may result in an increase in vessel diameter and a decrease in wall thickness but no change in cross-sectional area. The findings in the current study are consistent with the former mechanism and underscore the need to consider both wall thickness and vessel diameter in assessing the impact of interventions. Thus the results of the recent Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS), wherein both a diuretic and a dihydropyridine calcium channel blocker resulted in similar progression of the mean maximum carotid intimal-medial thickness and of "normal segments" (comparable to those evaluated in the present study), despite significant blood pressure reduction, may reflect remodeling of the arteries in response to successful blood pressure lowering as opposed to progressive "early atherosclerosis."<sup>50</sup>

**Study Limitations** Although the study population is relatively small, it constitutes one of the largest groups treated with ramipril as monotherapy in a double-blind randomized trial.<sup>14</sup> The duration of therapy was short, but was adequate in this and in a previous study<sup>51</sup> to show highly significant differences between ACE inhibition and a diuretic in changes in left ventricular mass. Hemodynamic load was assessed by measurement of both basal blood pressure and ambulatory blood pressure in the brachial artery; however, brachial blood pressure may differ from central aortic pressure to a variable extent. Furthermore changes in brachial blood pressure with pharmacologic therapy may not necessarily be indicative of changes in central aortic pressure or of the impact of therapy on the timing of reflected waves and thereby changes in augmentation of the pressure waveform.<sup>21</sup> Finally, the extent to which the ethnic characteristics of this largely nonwhite population influenced results is unknown in the absence of other data indicating racial differences

in the effectiveness of antihypertensive therapy in inducing regression of left ventricular hypertrophy.

In conclusion, the observed greater reduction in left ventricular mass associated with ACE inhibition in the current study and other studies and experimental data linking angiotensin II to myocardial growth, combined with the strong association of left ventricular mass with cardiovascular risk, may provide a pathophysiologic explanation for the ability of the renin profile to predict myocardial infarction in hypertensive patients.<sup>4-6</sup> Greater reduction of left ventricular mass may result in a more conclusive reduction in the cardiac complications of hypertension over the long term, particularly in view of preliminary evidence suggesting that reversal of left ventricular hypertrophy results in a reduction in cardiovascular events.<sup>52</sup> The impact of antihypertensive therapy on the hypertrophy of large vessels in human hypertensives remains uncertain. However, the results of the present study suggest that these arteries may show less true regression than does the left ventricle in response to relatively short-term blood pressure lowering.

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